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Tetrahedron Letters 46 (2005) 2373–2376

Tetrahedron Letters

Photochemical radical cyclization of γ,δ-unsaturated ketone oximes to 3,4-dihydro-2*H*-pyrroles

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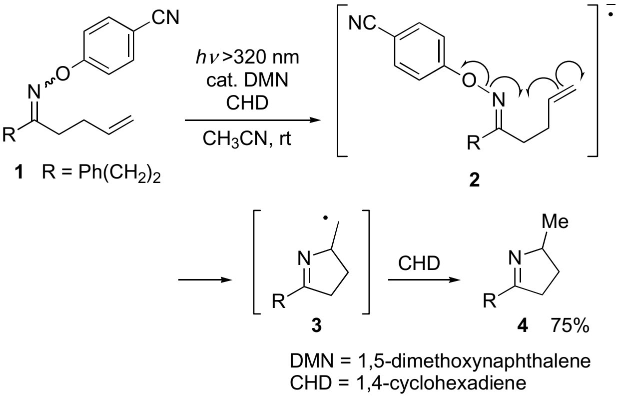
Received 7 January 2005; revised 9 February 2005; accepted 14 February 2005

Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—3,4-Dihydro-2*H*-pyrroles are synthesized from γ,δ-unsaturated oximes by photochemical radical cyclization with 1,5-dimethoxynaphthalene (DMN) as the sensitizer. The cyclization of alkyl ketone *O*-acetyloximes proceeds via photosensitized electron transfer in the presence of acetic acid, while conjugated oximes of aryl and α,β-unsaturated ketones are cyclized via energy transfer.

For the synthesis of nitrogen heterocycles, iminyl radical is employed as one of the reactive intermediates to prepare cyclic imines.[1] Several radical cyclization methods have been reported using iminyl radical species generated from oxime derivatives.[2–5] For example, Zard and co-workers reported the radical cyclization of *O*-acetyloximes[2e] by reduction with excess amount of nickel powder, Winreb and co-workers have developed the cyclization of *O*-2,6-dimethylbenzenesulfinyloximes by applying Hudson reaction.[2f] Although iminyl radicals are known to be generated from oximes by photo-induced energy transfer[4,6] or photochemical electron transfer,[5,7] these photochemical processes have not been utilized to radical cyclization except for few examples.[4,5]



Scheme 1. Photochemical cyclization of *O*-(*p*-cyanophenyl)oxime **1**.

During the course of our study on radical cyclization with oximes,[3] it was found that γ,δ-unsaturated ketone *O*-(*p*-cyanophenyl)oxime **1** cyclizes to 3,4-dihydro-2*H*-pyrrole **4** by radical process initiated by the single electron transfer from excited-1,5-dimethoxynaphthalene (DMN) (Scheme 1).[5] Thus formed anion radical **2** cyclizes to alkyl radical intermediate **3** with the elimination of *p*-cyanophenoxide, and **3** is trapped with 1,4-cyclohexadiene to yield cyclic imine **4**. To make electron transfer efficient, *p*-cyanophenyl group is introduced as a substituent of the oxime oxygen. It was desired to replace the cyanophenyl group to a small substituent in the sense of atom economy and for the availability of the starting material. In this letter, we wish to report an alternative photochemical cyclization of γ,δ-unsaturated oximes having acetyl (Ac) or methyl group on their oxime oxygen.

The photochemical radical cyclization of 3-butenyl phenethyl ketone *O*-acetyloxime (**5a**) was examined under UV irradiation in the presence of 1,5-dimethoxynaphthalene (DMN) as a sensitizer[8] in acetonitrile, using a 400 W high pressure lamp equipped with a UV cutoff filter ($h\nu > 300$ nm). Although *O*-acetyloxime **5a** was less reactive than *O*-(*p*-cyanophenyl)oxime **1** (entry

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Keywords: Oxime; Radical cyclization; Photoinduced electron transfer; Photoinduced energy transfer.

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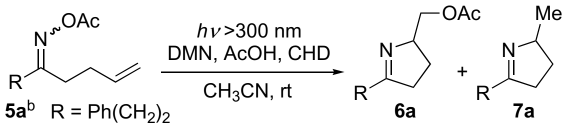
doi:10.1016/j.tetlet.2005.02.062

Table 1. Photochemical reaction of *O*-acetyloxime **5a**[a]



Entry	DMN/ equiv	AcOH/ equiv	CHD/ equiv	Time/h	Yield/%	
					6a	**7a**
1[c]	0.2	None	3.0	20	4	4
2	0.2	3.0	0.2	20	67	6
3	0.2	10	0.2	12	74	9
4[d]	None	3.0	0.2	20	—	—

[a] DMN = 1,5-dimethoxynaphthalene; CHD = 1,4-cyclohexadiene.

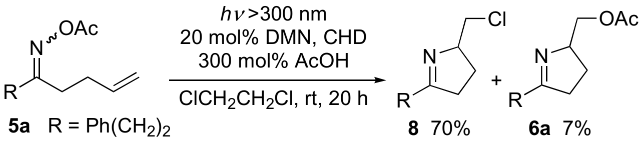
[b] *E*:*Z* = 1:1.

[c] Oxime **5a** was recovered in 86% yield.

[d] Oxime **5a** was recovered quantitatively.

1), addition of acetic acid (AcOH, 3 equiv) accelerated the reaction and dihydropyrrole **6a** was obtained in 67% yield (entry 2). When 10 equiv of AcOH was added, the cyclization finished after 12 h and the yield of **6a** was increased to 74% (entry 3). In both entries 2 and 3, a small amount of 1,4-cyclohexadiene was added, which reproduced the product yields of the cyclized products **6a** and **7a** satisfactorily, though the reason is not clear. The reaction did not proceed at all in the absence of the photosensitizer, DMN (entry 4, Table 1).

In 1,2-dichloroethane instead of acetonitrile, 2-chloromethyl dihydropyrrole **8** was obtained as a major product in 70% yield with a small amount of 2-acetoxymethyl derivative **6a** (Eq. 1). This result gave an important insight to consider the mechanism of this photochemical reaction as follows.



DMN = 1,5-dimethoxynaphthalene
CHD = 1,4-cyclohexadiene

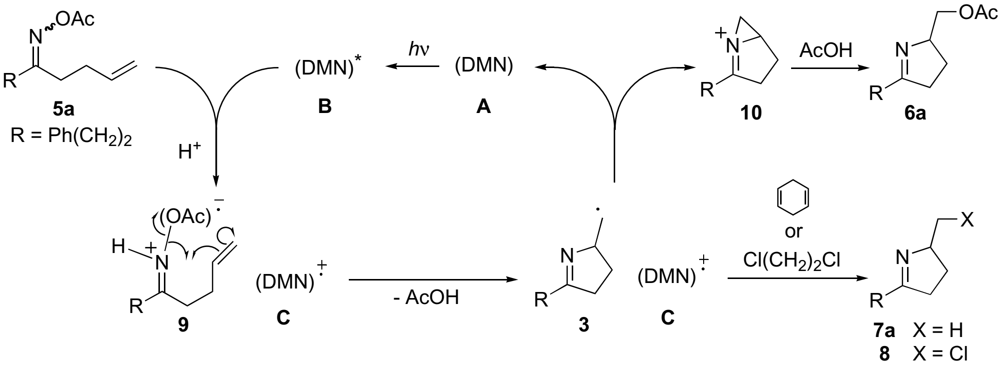
(1)

DMN is electron rich photosensitizer and has been used as a photochemical electron transfer reagent,[8] and *O*-acetyloxime **5a** may suffer from the reduction more easily by the protonation with AcOH. Thus, this cyclization is considered to proceed via photosensitized electron transfer as depicted in Scheme 2. Single electron transfer (SET) from excited DMN to protonated oxime **5a** affords cation radical of DMN **C** and radical species of protonated oxime **9**. Successively, cyclization occurs with the cleavage of the N–O bond to give alkyl radical species **3**. Back electron transfer (BET) from **3** to cation radical **C** regenerates the catalyst, DMN, generating cation species like **10**, which is trapped with AcOH immediately to give cyclic imine **6a**. Dihydropyrrole **7a** or **8** may be formed from radical species **3** by the capture of hydrogen or chloro atom from 1,4-cyclohexadiene or 1,2-dichloroethane, respectively.

The photochemical reaction was examined for various alkyl γ,δ-unsaturated *O*-acetyloximes as shown in Table 2. Although cyclization of **5a** having the terminal olefin gave cyclic imine **6a** and hydrogenated **7a** (entry 1), oximes **5b–d** having internal olefin gave exclusively acetoxymethyl imines **6b–d** in high yields (entries 2–4). From γ-methyl substituted oxime **5e**, pyridine **12** was formed via 6-*endo* cyclization in 15% with 58% total yield of 5-*exo* products **6e** and **7e** (entry 5).

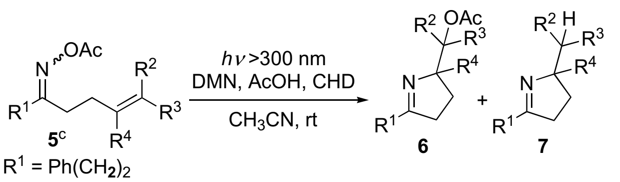
Next, the cyclization of aryl ketone oximes was examined instead of alkyl ketone oximes (Table 3). When phenyl ketone *O*-acetyloxime **13a** was irradiated under the same conditions, **13a** was consumed within 30 min and cyclization product **16a** and ketone **17** were obtained in 46% and 5% yields, respectively (entry 1). Without AcOH, the yield of dihydropyrrole **16a** was increased to 77% in the presence of excess amounts of 1,4-cyclohexadiene (entry 2). The reaction hardly proceeded in the absence of 1,5-dimethoxynaphthalene (entry 3). Interestingly, *O*-methyloxime **14a** and oxime **15** also cyclized to **16a** in good yields (entries 4 and 5).

Thus the reactions of phenyl ketone oximes **13–15** did not afford 2-(acetoxymethyl)dihydropyrrole and the addition of AcOH was not essential. These indicate that the cyclization of phenyl ketone oximes does not pro-



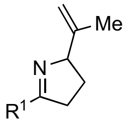
Scheme 2. Plausible mechanism of photochemical cyclization of **5a**.

Table 2. Photochemical cyclization of various *O*-acetyl oximes **5**[a,b]



Entry	R^2	R^3	R^4	Time/h	Yield/%	
1	H	H	H (**5a**)	12	73 (**6a**)	9 (**7a**)
2	H	Me	H (**5b**)[d]	13	82 (**6b**)[e]	0 (**7b**)
3	H	Ph	H (**5c**)	10	76 (**6c**)[f]	0 (**7c**)
4[g]	Me	Me	H (**5d**)	10	80 (**6d**)	0 (**7d**)
5[h]	H	H	Me (**5e**)	10	47 (**6e**)	11 (**7e**)

[a] DMN = 1,5-dimethoxynaphthalene; CHD = 1,4-cyclohexadiene.
[b] Oxime:DMN:AcOH:CHD = 1:0.2:10:0.2.
[c] *E*:*Z* = 1:1.
[d] The stereochemistry of olefin moiety was *E*:*Z* = 10:3.
[e] Diastereomer mixture (4:1).
[f] Diastereomer mixture (7:3).
[g] **11** was obtained in 10% yield.



11

[h] **12** was obtained in 15% yield.

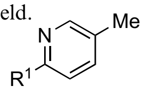


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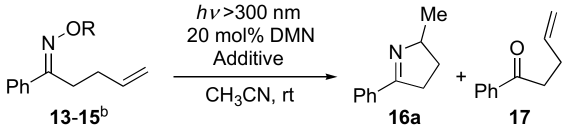
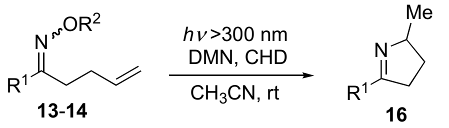
Table 3. Cyclization of phenyl ketone oximes **13**–**15**[a]

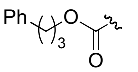
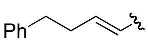
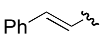


Entry	R	Additive (equiv)	Time/h	Yield/%	
				16a	**17**
1	Ac (**13a**)	CHD (3), AcOH (10)	0.5	46	5
2	Ac (**13a**)	CHD (10)	0.5	77	9
3[c]	Ac (**13a**)	CHD (10)	10	18	6
4	Me (**14a**)	CHD (10)	3	79	0
5	H (**15**)	CHD (10)	13	61	Trace

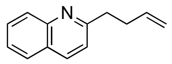
[a] DMN = 1,5-dimethoxynaphthalene; CHD = 1,4-cyclohexadiene.
[b] Only *E* isomers were used.
[c] The reaction was carried out in the absence of DMN. **13a** was recovered in 69% yield.

Table 4. Photochemical cyclization of conjugated ketone oximes[a,b]



Entry	R^1	R^2	*E*:*Z*	Time/h	Yield/%
1	Ph	Ac (**13a**)	1:0	0.5	77 (**16a**)
2		Me (**14a**)	1:0	3	79 (**16a**)
3		Piv (**13b**)	1:0	2	56 (**16b**)
4		Me (**14b**)	1:0	5	53 (**16b**)
5		Ac (**13c**)	3:7	2	12 (**16c**)
6		Me (**14c**)	3:5	9	56 (**16c**)
7[c]		Ac (**13d**)	3:8	5	63 (**16d**)
8[d]		Me (**14d**)	6:11	20	0 (**16d**)

[a] DMN = 1,5-dimethoxynaphthalene; CHD = 1,4-cyclohexadiene; Piv = pivaloyl.
[b] Oxime:DMN:CHD = 1:0.2:10.
[c] **18** was obtained in 12% yield.
[d] **18** was obtained in 5% yield.



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ceed by the electron transfer process. It is known that N–O bonds of aryl ketone *O*-acyloximes and aryl aldehyde *O*-alkyloximes are cleaved homolytically by photoexcitation,[6] and the absorption wavelength of the conjugated oximes is longer and the excitation energy is lower than those of saturated oximes generally.[9] Therefore, methyl dihydropyrrole **16a** is considered to be formed by energy transfer from the excited 1,5-dimethoxynaphthalene to phenyl ketone oxime **13**–**15**.[10] When the homolytic cleavage of the N–O bond occurs generating iminyl radical, the radical cyclization followed by hydrogen abstraction from 1,4-cyclohexadiene affords methyl dihydropyrrole **16a**.

The photochemical cyclization of some conjugated oximes of aryl ketone, α-keto ester, and α,β-unsaturated ketone was examined as shown in Table 4. Cyclic imines **16a**,**b** were obtained from phenyl ketone and α-keto ester *O*-acyloximes **13a**,**b** and *O*-methyloximes **14a**,**b** in moderate yields (entries 1–4). The cyclization of α,β-unsaturated ketone *O*-methyloxime **14c** proceeded, while the cyclization yield of *O*-acetyloxime of α,β-unsaturated ketone **13c** was low because the produced cyclic imine **16c** was not stable enough to the resulting acetic acid (entries 5 and 6). The reaction of *O*-methyloxime of styryl ketone **14d** did not afford the cyclization product **16d**, probably due to the excitation energy of styryl ketone *O*-methyloxime **14d**, which was not sufficient enough to cleave N–O bond of *O*-methyloxime **14d** (entry 8). Actually, cyclic imine **16d** was obtained in 63% yield from *O*-acetyloxime of styryl ketone **13d**, having a weaker N–O bond[6i] than the *O*-methyloxime **14d**, along with quinoline **18** produced via 6π cyclization (entry 7).

In conclusion, dihydropyrroles were synthesized from *O*-acetyl and *O*-methyl γ,δ-unsaturated oximes by two types of photochemical processes. Cyclization of alkyl ketone oximes is induced by the photochemical electron transfer from exited DMN, while conjugated ketone oximes are cyclized by the energy transfer from photoactivated DMN.

Acknowledgments

This research was supported by a Grant-in-Aid for The 21st Century COE Program for Frontiers in

Fundamental Chemistry from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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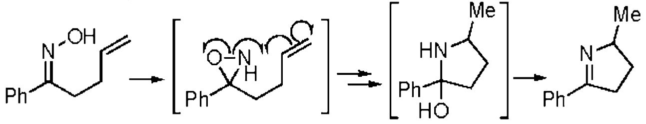
10. Cyclization of oxime **15** may proceed via homolytic N–O bond cleavage of oxime or formation of oxazirane **19**, which is the intermediate of the photochemical Beckmann rearrangement.



15 **19** **20** **16a**

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